

# Iron-Catalyzed Negishi Coupling Toward an Effective Olefin Synthesis

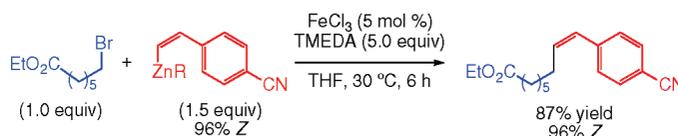
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## ABSTRACT



A selective iron-catalyzed cross-coupling of alkyl halides with alkenylzinc reagents is described. Primary and secondary alkyl chlorides, bromides, and iodides take part in the reaction to give the corresponding olefins in good to excellent yields in a stereospecific manner. High functional group compatibility is also demonstrated by using combinations of substrates possessing rather reactive substituents.

Nucleophilic substitution of alkyl electrophiles with alkenyl-metal reagents is a useful method for olefin synthesis. In particular, highly reactive alkenyl cuprates<sup>1,2</sup> can be coupled with a variety of primary alkyl tosylates, bromides, and iodides. This type of reaction has greatly contributed to total synthesis of natural products.<sup>3</sup> During the past decades, various cross-coupling reactions based on transition-metal catalysts have been demonstrated as an alternative for stoichiometric substitution: Fu and co-workers reported efficient palladium-<sup>4</sup> and nickel-catalyzed<sup>5</sup> cross-coupling reactions of primary alkyl halides with alkenyltin,<sup>4a,5b</sup> zinc,<sup>4b</sup> zirconium,<sup>4c</sup> and boron<sup>5a</sup> reagents. Recently, Oshima and co-

workers reported cobalt-catalyzed cross-coupling of primary and secondary alkyl halides with 1-(trimethylsilyl)ethenyl-magnesium reagent.<sup>6</sup> Nevertheless, there remain much to be improved, for example, low selectivity and yield for alkyl chlorides or secondary electrophiles.<sup>7</sup>

Iron catalysis has been intensively studied in the field of cross-coupling reactions,<sup>8–10</sup> and certain combinations of iron salts and additives, such as FeCl<sub>3</sub>/*N,N,N',N'*-tetramethylethylenediamine (TMEDA)<sup>10a,11</sup> and Fe(acac)<sub>3</sub>/TMEDA/hexamethylenetetramine (HMTA),<sup>10g,12</sup> have proven to be effective for the cross-coupling of alkyl halides with alkenylmagnesium reagents. Despite the recent progress, several issues, such as functional group compatibility, a limited substrate scope, and moderate yield and stereospecificity are still to be solved in order to achieve efficient stereocontrolled olefin synthesis by the iron-catalyzed alkenyl coupling. Herein, we report a simple and effective protocol for olefin

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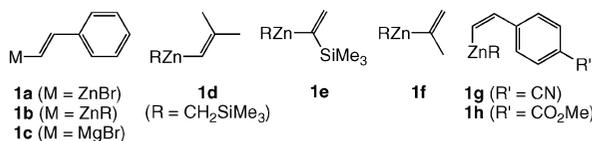
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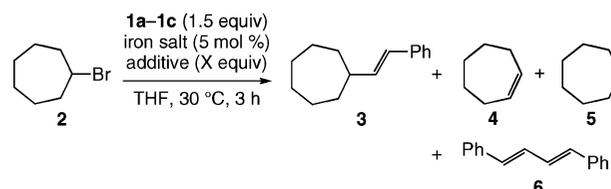
synthesis where readily available alkenylzinc reagents and a wide variety of alkyl halides, including chlorides, are cross-coupled by an iron catalyst in the presence of excess TMEDA.



**Figure 1.** Alkenyl metal reagents examined for the iron-catalyzed cross-coupling with alkyl halides.

We conducted the reaction of a secondary alkyl bromide with alkenylzinc reagents (**1a** and **1b**) for screening of iron precatalyst and additives (Table 1).<sup>13,14</sup> The reaction between **1a** and **2** proceeded very sluggishly in the presence of 5 mol % of FeCl<sub>3</sub> to give the desired coupling product **3** in 8% yield with recovery of 70% of the bromide **2** (entry 1).  $\beta$ -Styryl[(trimethylsilyl)methyl]zinc reagent **1b**, prepared from **1a** and (trimethylsilyl)methylmagnesium chloride<sup>13a,e,15</sup> showed slightly higher reactivity, albeit lower selectivity, to

**Table 1.** Cross-Coupling of Styryl Metals (RM) with Bromocycloheptane (**2**) in the Presence of Iron Salt and Additive



entry <sup>a</sup>	RM <sup>b</sup>	iron salt	additive (X equiv)	yield (%) <sup>c</sup>			RSM <sup>d</sup> (%) <sup>c</sup>	6 (mmol)
				3 <sup>e</sup>	4	5		
1	<b>1a</b>	FeCl <sub>3</sub>	none	8	< 1	1	70	0.05
2	<b>1b</b>	FeCl <sub>3</sub>	none	25	4	17	0	0.12
3	<b>1b</b>	FeCl <sub>3</sub>	TMEDA (1.5)	56	4	13	0	0.11
4	<b>1b</b>	FeCl <sub>3</sub>	TMEDA (3.0)	91	< 1	3	0	0.10
5	<b>1b</b>	FeCl <sub>3</sub>	TMEDA (3.5)	95	< 1	3	0	0.08
6	<b>1b</b>	Fe(acac) <sub>3</sub>	TMEDA (3.5)	85	0	3	10	0.06
7	<b>1b</b>	FeCl <sub>2</sub>	TMEDA (3.5)	97	< 1	3	0	0.05
8 <sup>f</sup>	<b>1c</b>	FeCl <sub>3</sub>	TMEDA (3.5)	35	12	4	35	0.02

<sup>a</sup> Reactions were carried out on a 0.5 mmol scale. <sup>b</sup> Prepared from  $\beta$ -bromostyrene (*E/Z* = 86/14). <sup>c</sup> Yields were determined by GLC analysis using undecane as an internal standard. <sup>d</sup> Recovery of starting bromide. <sup>e</sup> *E/Z* = 80/20. <sup>f</sup> **1c** was added dropwise over 0.5 h at 0 °C.

give **3** in 25% yield along with byproducts (**4** in 4% and **5** in 17% yield) (entry 2). In these cases, formation of diene **6** was observed in the initial period of the reaction.<sup>16</sup> Note that high molecular-weight byproducts, derived from bromocycloheptane **2** and the diene **6**, formed in moderate yields.<sup>17</sup>

During the screening of additives, we found that the amount of TMEDA was critical in achieving a selective coupling reaction: the reaction with 3.5 equiv of TMEDA gave **3** in 95% yield, while the reaction with 1.5 and 3.0 equiv of TMEDA gave **3** in 56% and 91% yield, respectively (entries 3–5).<sup>18</sup> Because TMEDA can coordinate not only to the iron atom but also to the zinc and magnesium atoms, it would be necessary to use a stoichiometric or slight excess amount of TMEDA relative to the total amount of metal salts to ensure that TMEDA coordinates the iron catalyst. The divalent iron precursor, FeCl<sub>2</sub>, as well as Fe(acac)<sub>3</sub> was comparable to FeCl<sub>3</sub> (entries 6 and 7). Note that the reaction with alkenylmagnesium reagent **1c** in the presence of 3.5 equiv of TMEDA was far less selective (entry 8). The conditions reported for alkenylmagnesium reagents<sup>11,12</sup> were not effective for the reaction between **1c** and **2** (see the Supporting Information).

Table 2 illustrates the scope of the coupling reaction between various alkyl halides and alkenylzinc reagents

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**Table 2.** Cross-Coupling of Alkenylzinc Reagents and Alkyl Halides

entry <sup>a</sup>	R <sup>1</sup> -X	R <sup>2</sup> Zn	product	yield (%) <sup>b</sup> conditions
1				<b>98</b> (X = I) 30 °C, 15 h
2	C <sub>10</sub> H <sub>21</sub> -X	<b>1d</b>		<b>89</b> (X = Br) 40 °C, 18 h
3 <sup>c</sup>				<b>80</b> (X = Cl) 50 °C, 24 h
4 <sup>d</sup>				<b>95<sup>e</sup></b> (X = I) 30 °C, 18 h
5		<b>1d</b>		<b>99<sup>e</sup></b> (X = Br) 30 °C, 24 h
6 <sup>d</sup>				<b>91<sup>e</sup></b> (X = Cl) 40 °C, 24 h
7 <sup>d</sup>		<b>1d</b>		<b>96<sup>e</sup></b> 30 °C, 18 h
8 <sup>d</sup>		<b>1d</b>		<b>91<sup>e</sup></b> 30 °C, 18 h
9 <sup>d</sup>		<b>1e</b>		<b>79</b> 40 °C, 24 h
10 <sup>d</sup>		<b>1e</b>		<b>83</b> 30 °C, 48 h
11	NC-(CH <sub>2</sub> ) <sub>5</sub> -Br	<b>1d</b>	NC-(CH <sub>2</sub> ) <sub>5</sub> -CH=CH-CH <sub>3</sub>	<b>95</b> 30 °C, 3 h 40 °C, 6 h
12 <sup>d</sup>	AcO-(CH <sub>2</sub> ) <sub>5</sub> -Br	<b>1f</b>	AcO-(CH <sub>2</sub> ) <sub>5</sub> -CH=CH-CH <sub>3</sub>	<b>97</b> 30 °C, 3 h
13 <sup>d</sup>		<b>1f</b>		<b>95</b> 30 °C, 3 h
14		<b>1d</b>		<b>73</b> 30 °C, 48 h
15		<b>1b'</b>		<b>86<sup>g</sup></b> 30 °C, 6 h

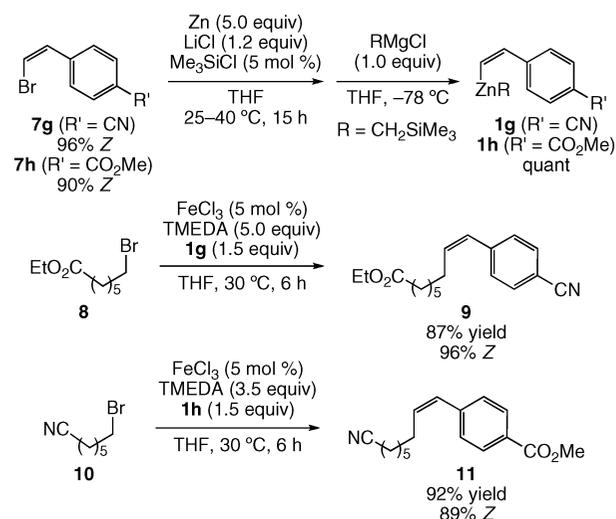
<sup>a</sup> Reactions were carried out according to the procedure for entry 5 in Table 1 on a 1.0 mmol scale. <sup>b</sup> Isolated yield. <sup>c</sup> Three equivalents of **1d** was used. <sup>d</sup> Two equivalents of **1d-f** was used. <sup>e</sup> NMR yield. <sup>f</sup> E/Z = 93/7. <sup>g</sup> E/Z = 90/10.

(**1b,d-f**, Figure 1) under the present conditions. As shown in entries 1–8, the reactions of primary and secondary alkyl halides with (2-methylprop-1-enyl)zinc reagent **1d** smoothly proceeded at 30–40 °C to give the desired product in good to excellent yields. It is noteworthy that a variety of alkyl chlorides, which resulted in low yielding according to the previous reports, take part in the alkenyl coupling (entries 3 and 6–8). In all the cases examined, the reduction byproduct (alkane) was obtained in 1–3% yields as a minor side product, and the elimination byproduct (alkene) was almost negligible. 1-(Trimethylsilyl)vinylzinc reagent **1e**, slightly less reactive than **1d**, can be cross-coupled with secondary alkyl halides in good yields (entries 9 and 10). Alkyl bromides possessing a functional group, such as cyano,

acetoxy, and carbamate, participate in the coupling reaction (entries 11–13).

1-Bromo-4-(2-bromoethyl)benzene possessing two potential reactive sites, Csp<sup>2</sup>-Br and Csp<sup>3</sup>-Br, reacted with **1d** via a selective Csp<sup>3</sup>-Br bond cleavage (entry 14). The selective cleavage can be explained by the radical character of the catalytically active organoiron species. The intermediacy of alkyl radicals was supported by the reaction of (bromomethyl)cyclopropane with **1b**, which gave the ring-opening diene as the sole cross-coupling product (entry 15).

The present method is stereospecific and chemoselective, as demonstrated in Scheme 1. (*Z*)-(4-Cyanostyryl)zinc reagent **1g**, prepared from (*Z*)-4-(2-bromovinyl) benzonitrile **7g** (96% *Z*) in two steps,<sup>19</sup> was thus coupled with ethyl 7-bromoheptanoate **8** under the conditions described above to give **9** in 87% yield without any loss of geometrical purity (96% *Z*). Similarly, the reaction between (*Z*)-(4-methoxycarbonylstyryl)zinc reagent (90% *Z*) **1h** and 7-bromoheptanenitrile **10** took place stereoselectively to give **11** in 92% yield (89% *Z*). The cyano and alkoxy carbonyl groups remained untouched.<sup>20</sup>

**Scheme 1.** Stereospecific Negishi Coupling between a *Z*-Alkenylzinc Reagent and an Alkyl Bromide Both Bearing a Functional Group

In summary, we have demonstrated that the iron-catalyzed cross-coupling reaction of primary and secondary alkyl halides with alkenylzinc reagents provides the corresponding olefins in a highly selective manner. The present method is high-yielding, chemoselective, stereospecific, and free of rare metals and phosphine ligands, and it shows its potential in efficient and versatile access to functional molecules bearing a carbon–carbon double bond.

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(20) Aliphatic ketones underwent deprotonation under the reaction conditions and interfered with the cross-coupling reaction (data not shown).

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**Supporting Information Available:** Experimental procedures and physical properties of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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